Growth kinetics of circular liquid domains on vesicles by diffusion-controlled coalescence

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Abstract. Motivated by recent experiments on multi-component membranes, the growth kinetics of domains on vesicles is theoretically studied. It is known that the steady-state rate of coalescence cannot be obtained by taking the long-time limit of the coalescence rate when the membrane is regarded as an infinite two-dimensional (2D) system. The steady-state rate of coalescence is obtained by explicitly taking into account the spherical vesicle shape. Using the expression of the 2D diffusion coefficient obtained in the limit of small domain size, an analytical expression for the domain growth kinetics is obtained when the circular shape is always maintained. For large domains, the growth kinetics is discussed by investigating the size dependence of the coalescence rate using the expression for the diffusion coefficient of arbitrary domain size.

1. Introduction

Lipid bilayer membranes can be regarded as two-dimensional (2D) systems embedded in three-dimensional (3D) solvent. The membranes are coupled to solvent since the lipids composing the membrane interact with solvent surrounding it and the momentum can be exchanged between the membrane and the solvent [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. In this sense, membranes can be regarded as quasi-2D systems. By the recent advances in experiments, domains formed by phase separation in multicomponent membranes are visualized, and the lipid spatial organization and its dynamics have been studied [11, 12, 13, 14, 15]. The phase separation kinetics and coarsening are influenced by the dimensionality, domain shapes and the hydrodynamics in the systems [16]. The phase separation in multicomponent lipid bilayer exhibits rich dynamics partly due to the momentum dissipation to the third-dimensions while the motion is confined to 2D [7, 8, 9].

In recent experiments, the growth kinetics of circular domains on ternary fluid vesicles has been observed by fluorescence microscopy [11, 13, 14]. In these experiments, liquid domains are formed in giant vesicles by phase separation into the liquid-ordered phase and the liquid-disordered phase on lowering the temperature from the one-phase region. Yanagisawa *et al.* found two different types of domain coalescence kinetics [14]. In one of the coalescence processes, the domains grew by collision and coalescing while keeping the circular shape until the large domains of the vesicle size appeared. This growth kinetics due to the diffusion-controlled coalescence (DCC) was described by a power-law. In the other coalescence process, the domain growth was suppressed by membrane-mediated repulsive inter-domain interactions. Recently, it was pointed out that the domain coalescence could be prevented by the membrane-mediated interactions between liquid domains associated with the deformations of the membrane [17, 18, 19, 20, 21]. When the liquid domain size exceeds a critical value, the boundary line energy is reduced by budding at the expense of some bending energy. The significant slowing down of the domain growth can be observed for large budded domains [14, 21]. In the steady state, the domain patterns and the membrane shapes can be stabilized by the coupling between the local membrane curvature and the line tension [12, 15, 22, 23, 24].

As briefly summarized above, the liquid domains coarsen under the influence of several competing processes. Even without budding, the observed growth kinetics was different from that obtained from the scaling hypothesis [13, 14]. Motivated by the experiments, we study theoretically the growth kinetics of domains on vesicles by DCC.

The study of domain growth on vesicle surfaces is still limited compared to that in 3D [16]. According to the scaling hypothesis, the domain growth exponent due to DCC in 2D is 1/2 in contrast to that in 3D given by 1/3 [25, 26]. However, it should be noted that, in the scaling hypothesis, the coalescence process is not explicitly taken into account. Moreover, it is known that the steady-state rate of coalescence cannot be obtained for an infinitely large 2D system [27, 28]. In contrast to diffusion in 3D space,

the boundary conditions are crucial to obtain the coalescence rate when the diffusion is restricted in 2D. This point is missing in the scaling hypothesis.

In addition to the above argument on pure 2D systems, the coalescence of liquid domains can be influenced by the coupling between the membrane and the solvent. The diffusion of large domains is more influenced by the coupling compared to that of small domains. As the domain grows, the influence of the coupling between the membrane and the solvent increases. The domain growth kinetics has been studied by dissipative particle dynamics simulations and continuum simulations [7, 8, 9, 29]. The simulation results suggest the slowing down of the domain growth by DCC due to the coupling [7].

In this paper, we study the growth of liquid domains immersed in a 2D membrane by using an analytical theory which goes beyond the scaling hypothesis. We note that the steady-state rate of coalescence can be obtained by taking into account explicitly the vesicle shape [30, 31]. By using the diffusion coefficient of domains obtained by taking into account the coupling between the membrane and the solvent [1, 2, 3, 4, 5, 6, 10], we show that it is independent of the domain size in the limit of small domain size. In such a case, it is known that the size distribution is described by the Smoluchowski theory of coalescence processes [32]. By further assuming that the circular shape of the liquid domains is always maintained, the time evolution equation of the mean domain size is obtained from the size distribution using the conservation of domain area upon coalescence. The mean domain growth is expressed by a single function for the whole time regime starting from the initial induction period of coalescence to the final asymptotic regime given by the power-law. When the domain size is large, we discuss the influence of the coupling between the membrane and the solvent on the domain growth by analyzing the size dependence of the coalescence rate.

In Sec. 2, we present the known results obtained from the scaling hypothesis. In Sec. 3, the results of Smoluchowski theory in pure 3D and 2D infinite systems are reviewed. In Sec. 4, the coalescence rate is obtained by taking into account the vesicle shape. In Sec. 5, the analytical expression representing the growth of mean domain size is obtained when the circular shape and the area of the liquid domains are kept before and after the coalescence. The size dependence of the the coalescence rate is investigated by using the analytical expression of the diffusion coefficient for the liquid domain of the arbitrary size in Sec. 6. In Sec. 7, the theoretical results are discussed in relation to those obtained by the recent experiments [14].

2. Scaling theory

In this section, we summarize the results obtained from the scaling theory. The scaling theory is the simplest way to derive the power-law growth of domain size. Obviously, one cannot obtain both the transient growth leading to the asymptotic power-law kinetics and the magnitude of the power-law growth.

The scaling theory is based on the hypothesis that the mean domain radius $\langle a(t) \rangle$

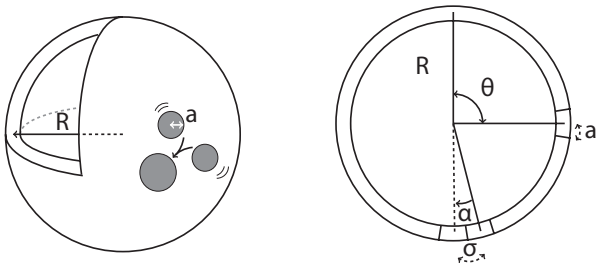

Figure 1. Schematic picture liquid domains embedded in a fluid vesicle (left). The radius of liquid domains is a while the vesicle radius is R. Liquid domains undergo Brownian motion on the vesicle surface. Shown on the right is the geometrical parametrization. θ denotes the azimuthal angle and α is the angle between domain centers at collision. σ represents the encounter distance.

in d-dimension is related to time t by

$$\langle a(t)\rangle^2 \sim D_d t, \tag{1}$$

where D_d is the diffusion coefficient and subscript d denotes the dimensionality. In 3D, the diffusion coefficient of the domain is inversely proportional to $\langle a(t)\rangle$ by the Stokes-Einstein relation, $D_3 \sim 1/\langle a(t)\rangle$. By substituting this relation in the scaling relation, we obtain $\langle a(t)\rangle \sim t^{1/3}$ [16, 25, 26]. For 2D, we have $D_2 \sim k_{\rm B}T/\eta$ by the dimensional argument, where $k_{\rm B}$ is the Boltzmann constant, T the temperature, η the 2D membrane viscosity surrounding the domain. By using the above expression of D_2, the scaling hypothesis leads to $\langle a(t)\rangle \sim t^{1/2}$ [16, 25, 26]. It should be pointed out that a logarithmically time-dependent diffusion coefficient was derived in pure 2D by the hydrodynamic theory [2]. When the membrane couples to the solvent, a constant diffusion coefficient was derived, and D_2 depends logarithmically on the domain size in the weak coupling limit [1, 2]. The logarithmic size dependence and the numerical factors are ignored in the dimensional argument.

We also note that the time given by $\langle a(t)\rangle^2/D_d$ is not equal to the coalescence time of the domain with size $\langle a(t)\rangle$. The coalescence time should be given by the mean first time that domains coalesce by diffusion from random initial distribution. Below, we show that the latter time is different from the one given by $\langle a(t)\rangle^2/D_d$.

The scaling hypothesis merely relates a single length scale given by the mean domain size at time t with the diffusion coefficient as shown in Eq. (1) and it should be justified. In the subsequent sections, we point out that the results of the scaling hypothesis cannot be obtained for the domain growth by the diffusion-coalescence in 2D infinite systems. Then, we show that the scaling hypothesis is consistent with the domain growth kinetics by diffusion-coalescence when the available diffusion area is finite in 2D. The whole kinetics including transient growth and the final power-law growth will be obtained by taking into account the diffusion-coalescent process and the vesicle shape explicitly.

3. Smoluchowski theory in infinite systems

In the Smoluchowski theory, domain motion is assumed to be independent of the others and coalescence between a pair of domains is considered. When both domains can move, it is difficult to solve the problem analytically. We assume that one of the domains is fixed and the other diffuses with the mutual diffusion coefficient D_d which is the sum of the diffusion coefficients of two spherical domains of equal size [33]. Coalescence takes place immediately when two domains come in contact at the encounter distance which is the sum of the radii of the two domains. In the theoretical formulation, the spatial distribution of domains satisfies the diffusion equation and the spatial domain density should vanish at the encounter distance. The domain size increases immediately after the coalescence and the spatial distribution of the new domain size should be zero at the encounter distance for the increased domain size.

The density of mobile domain around the immobile domain satisfies the diffusion equation

$$\frac{\partial}{\partial t}\rho_d(r,t) = D_d\nabla^2\rho_d(r,t), \tag{2}$$

where r is the distance to the center of the immobile domain. We assume random initial condition given by,

$$\rho_d(r, t=0) = 1. \tag{3}$$

The boundary condition applied at the encounter distance σ is given by

$$\rho_d(r=\sigma, t) = 0. \tag{4}$$

We should set another boundary condition such that the density at infinite separation is unity, i.e.,

$$\lim_{r\to\infty}\rho_d(r,t) = 1. \tag{5}$$

3.1. Three-dimensions (3D)

Before investigating the domain growth on the 2D spherical surface, we shall briefly present the known results for 3D infinite systems and show that the corresponding results do not hold for 2D cases.

For 3D infinite systems, the density profile which satisfies both of the boundary conditions is $\rho_3(r) = 1 - (\sigma/r)$ [33]. The mean coalescence rate is given by the inward flow of domains across the surface at σ

$$k_3 = 4\pi\sigma^2 D_3\left(\frac{\mathrm{d}\rho_3(r)}{\mathrm{d}r}\right)_{r=\sigma} = 4\pi\sigma D_3. \tag{6}$$

In a 3D fluid of viscosity η_s, the diffusion coefficient is inversely proportional to the size of the diffusing object, $D_3 = k_\mathrm{B}T/3\pi\eta_\mathrm{s}\sigma$. By using this Stokes-Einstein relation, the mean coalescence rate can be expressed by $k_3 = 4k_\mathrm{B}T/3\eta_\mathrm{s}$. Notice that $\sigma/2$ is the radius of the spherical domain [32].

3.2. Two-dimensions (2D)

By applying the boundary condition at σ, we obtain

$$\rho_2(r) = C \ln(\sigma/r), \tag{7}$$

where C is a constant determined from the other boundary condition at $r \to \infty$. However, it is impossible to fix C because $\rho_2(r)$ diverges for $r \to \infty$ as long as C is finite. Unlike 3D infinite systems, the density cannot satisfy both boundary conditions, Eqs. (4) and (5), simultaneously.

4. Smoluchowski theory in spherical surface

The difficulty mentioned in the previous section for 2D can be overcome if the available diffusion area is finite. The density profile depends crucially on the shape of the 2D region. In the experiments [14], DCC of circular domains was observed on the vesicle surfaces. In principle, the coalescence rate can be obtained by modifying the method shown in the previous section applicable to the spherical region but the calculation is rather complicated. In this paper, we employ an alternative method.

In the method, we investigate the life time of the density of mobile domains survived from collision to the immobile domain. In a confined region, the decay of the density can be well approximated by a single exponential. The time constant of the exponential decay can be reasonably obtained from the mean first-passage time of a mobile domain to the periphery of the immobile domain by assuming uniform distribution for the starting point. For the coalescence, the mean first-passage time is the mean coalescence time corresponding to the encounter time between two domains. When the initial position of the mobile reactant is $z = \cos\theta$ (see Fig. 1 for the geometry), the mean coalescence time $\tau(z)$ satisfies the following equation (see the Appendix for the derivation) [30]

$$\frac{D_2}{R^2}\frac{\partial}{\partial z}(1-z^2)\frac{\partial}{\partial z}\tau(z) = -1. \tag{8}$$

The boundary conditions are

$$\tau(z = -\cos\alpha) = 0, \qquad \left(\frac{\partial \tau(z)}{\partial z}\right)_{z=1} = 0, \tag{9}$$

where α is the angle between domain centers at collision (see Fig. 1). Notice that a simple geometric argument gives $\sin(\alpha/2) = \sigma/(2R)$ and $\cos\alpha = 1 - \sigma^2/(2R^2)$ [30]. Equations (8) and (9) can be easily solved, and we obtain

$$\tau(z) = \frac{R^2}{D_2} \ln\left[\frac{2R^2}{\sigma^2}(1+z)\right]. \tag{10}$$

By averaging over the random initial distribution, we obtain [30]

$$\tau_{\rm av} = \frac{\int_{-\cos\alpha}^{1} {\rm d}z\, \tau(z)}{2 - \sigma^2/(2R^2)} = \frac{R^2}{D_2}\left[\frac{2}{1-(\sigma/2R)^2}\ln\left(\frac{2R}{\sigma}\right) - 1\right]. \tag{11}$$

The probability that the mobile domain has not reached the immobile domain up to time t is given by $\exp(-t/\tau_{\rm av})$ when domains are initially distributed uniformly

in the spherical surface. The same probability can be expressed by using the bulk bimolecular rate as $\exp(-k_d t/A)$, where the surface area available for diffusion is $A = 2\pi R^2[2-\sigma^2/(2R^2)]$. Comparing these expressions, we find that the bulk bimolecular rate can be calculated from the mean coalescence time by $k_2 = A/\tau_{\rm av}$ [30, 31, 34].

With the use of the bimolecular rate, the mean coalescence rate is obtained as [30, 31, 34]

$$k_2 = \frac{4\pi[1-(a/R)^2]D_2(a)}{2\ln(R/a)-1+(a/R)^2} \tag{12}$$

$$\simeq \frac{4\pi D_2(a)}{2\ln(R/a)-1}, \tag{13}$$

where $a \ll R$ is used to obtain the second equality. The mutual diffusion coefficient is now expressed by $D_2(a)$ since it depends on the domain radius a as shown below.

Unfortunately, the full size-dependence of the diffusion coefficient is not known for spherical vesicles. However, the analytical expression is known for a circular liquid domain which has the same viscosity as the outside of the domain for 2D flat membranes. In this case, the mutual diffusion coefficient was obtained by De Koker as [3]

$$D_2(a) = \frac{2k_{\rm B}T}{\pi\eta}\int_0^\infty {\rm d}z\,\frac{J_1^2(z)}{z^2(z+\nu a)}, \tag{14}$$

when the two circular domains have the same radius a. In the above, $J_1(z)$ is the Bessel function of the first kind, η is the 2D membrane viscosity, $\nu = 2\eta_{\rm s}/\eta$ with $\eta_{\rm s}$ being the viscosity of the outer fluids. Here we have assumed that the viscosities of the liquid inside and outside the vesicle are the same. The analytical expression after the integration can be expressed using Meijer G-functions [6, 5]. In the case of $\nu a \ll 1$, the above expression reduces to [6, 5]

$$D_2(a) \approx \frac{k_{\rm B}T}{\pi\eta}\left[\ln\left(\frac{2}{\nu a}\right)-\gamma+\frac{1}{4}\right], \tag{15}$$

where $\gamma = 0.5772\cdots$ is Euler's constant. Equation (15) is slightly larger than the mutual diffusion coefficient of the Saffman-Delbrück (SD) theory derived for solid domains under the condition of $\nu a \ll 1$. Strictly speaking, the SD result was also obtained for 2D flat membranes. Recently, it was shown that the SD result was applicable for spherical vesicles when $a < R < 1/\nu$ [36].

By substituting Eq. (15) into Eq. (13), we obtain

$$k_2 \approx \frac{k_{\rm B}T}{\eta}, \tag{16}$$

when $a/R \ll 1$. The coalescence rate is independent of a in this limit. Then $k_2 t$ approximately represents the area explored by a diffusive object of radius σ during time t [34, 35]. Hence $k_2 t$ is given by $D_2(a)t$ times the effective collision cross-section. The size independence is the result of the two opposing effects; with increasing the domain size, the diffusion coefficient decreases while the effective collision cross-section given by $4\pi/[2\ln(R/a)-1]$ in Eq. (13) increases.

Strictly speaking, the coalescence rate depends on the domain size if the coalescence occurs between domains having different sizes. However, such a size dependence is small for 2D because of the weak logarithmic dependence in Eqs. (13) and (15), and will be ignored hereafter. In fact, the size dependence was not taken into account even to study the coalescence processes in 3D [32].

Equation (12) is valid even if the condition $a/R \ll 1$ is not satisfied. The full size-dependence of the coalescence rate will be studied by substituting Eq. (14) into Eq. (12) as we shall discuss in Sec. 6.

5. Growth kinetics of liquid domains

Now we consider the formation of m-fold domains from the initial domains with the same size. When the coalescence rate is independent of the domain size as discussed above, the number density of m-fold domain $n_m(t)$ at time t is given by [32]

$$\frac{n_m(t)}{n_1} = \frac{(t/\tau)^{m-1}}{(1+t/\tau)^m}, \tag{17}$$

where

$$\tau = \frac{1}{k_d n_1}, \tag{18}$$

and n_1 is the initial number density of the primary domains, and k_d the coalescence rate in d-dimensional space.

In general, if the aggregates of large sizes are in the solid state, there are many possible shapes of aggregates. The shape characterization and the size distribution have been studied in the conventional theory of Brownian coagulation. Here, we study Brownian coalescence of liquid domains under the condition that the circular shape is always maintained. For comparison, we also consider Brownian coalescence of liquid domains in 3D infinite systems, where the spherical shape is always maintained. Under this assumption, the time evolution of the domain size can be obtained analytically.

By assuming that the domain shape is immediately restored after the coalescence, the radius of the m-fold domain a_m is determined by the area ($d = 2$) or volume ($d = 3$) conservation relation,

$$a_m^d = m a_1^d. \tag{19}$$

By averaging a_m over the distribution of m-fold aggregate [see Eq. (17)], the mean domain radius $\langle a(t) \rangle$ at time t is obtained as

$$\frac{\langle a(t) \rangle}{a_1} = \sum_{m=1}^{\infty} m^{1/d} \frac{n_m(t)}{n_1} = \frac{\tau}{t} \mathrm{Li}_{-1/d}\left(\frac{t/\tau}{1+t/\tau}\right). \tag{20}$$

In the above, we have used the polylogarithm function defined by [37]

$$\mathrm{Li}_s(x) = \sum_{k=1}^{\infty} \frac{x^k}{k^s}. \tag{21}$$

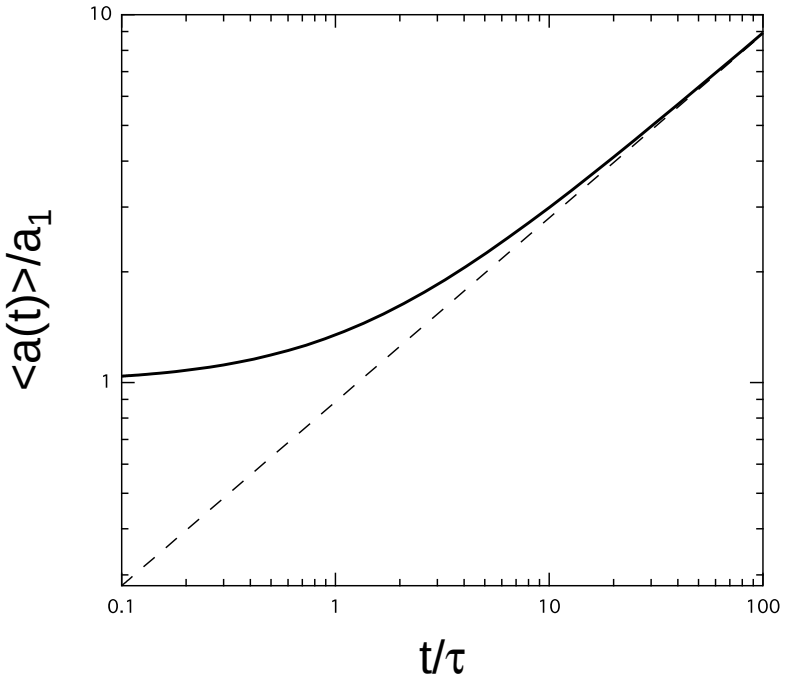

Figure 2. The average domain size $\langle a(t)\rangle/a_1$ as a function of dimensionless time t/τ when domains are confined in the spherical surface. The solid line is obtained from Eq. (20) and the dashed line represents the asymptotic behavior given by Eq. (22).

In the asymptotic limit of $t/\tau \gg 1$, Eq. (20) reduces to either

$$\frac{\langle a(t)\rangle}{a_1} \approx \frac{\sqrt{\pi}}{2}\left(\frac{t}{\tau}\right)^{1/2} \tag{22}$$

for the coalescence in 2D spherical surfaces, or

$$\frac{\langle a(t)\rangle}{a_1} \approx \Gamma\left(\frac{4}{3}\right)\left(\frac{t}{\tau}\right)^{1/3} \tag{23}$$

for that in 3D infinite systems. Here $\Gamma(x)$ is the gamma function. The time evolution of $\langle a(t)\rangle/a_1$ is shown in Fig. 2 for the domain coalescence on the vesicle. The asymptotic time dependence is well approximated by Eq. (22) when $t/\tau \gg 1$. We can see the induction period of coalescence when $t/\tau < 1$. The induction period is characterized by the inverse of the apparent coalescence rate given by the coalescence rate times the initial number density of the primary domains, Eq. (18). By taking into account explicitly the vesicle shape, the finite coalescence rate is obtained from the Smoluchowski theory and the results show the induction period before the asymptotic growth.

6. Size dependence of the coalescence rate

In the previous section, the growth kinetics of the circular liquid domain by diffusion coalescence is obtained when the coalescence rate is independent of the size of the liquid domain. The result for the domain growth on the vesicle is obtained in the limit of

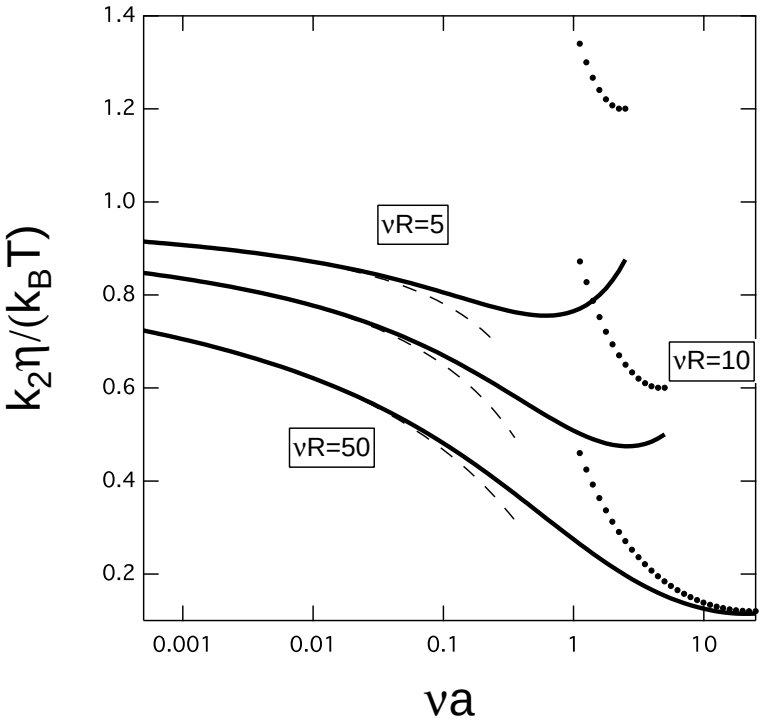

Figure 3. $k_2\eta/(k_{\rm B}T)$ as a function of the dimensionless domain size νa. The solid line is obtained from Eq. (12) using the expression of the diffusion coefficient for a circular liquid domain which has the same viscosity as the outside of the domain. $R\nu = 5$, 10 and 50 from top to bottom. The dashed lines are obtained by substituting Eq. (15) into Eq. (12). The dots are obtained by substituting Eq. (24) into Eq. (12).

$\nu a \ll 1$. Below, we study the size dependence of the coalescence rate using Eqs. (12) and (14). The diffusion coefficient Eq. (14) is obtained for a circular liquid domain of arbitrary size. In the limit of $\nu a \ll 1$, the domain size dependence of the diffusion coefficient is logarithmic as shown by Eq. (15). The coalescence rate is given by $k_{\rm B}T/\eta$ independent of the domain size because of the cancellation of the logarithmic domain size dependence both in Eqs. (12) and (15). In the opposite limit of $\nu a \gg 1$, the diffusion coefficient is obtained as [5, 6]

$$D_2(a) \approx \frac{8k_{\rm B}T}{3\pi^2\eta_{\rm s}a}, \tag{24}$$

which is inversely proportional to the domain radius a.

The coalescence rate obtained by substituting Eq. (14) into Eq. (12) is shown by the solid lines in Fig. 3. For relatively small vesicle, say $\nu R = 5$, the coalescence rate is almost independent of the domain size and is approximately given by $k_{\rm B}T/\eta$. The situation is very different for large vesicles. When $\nu R \geq 10$, the size dependence of the coalescence rate can be ignored only when $\nu a < 0.1$. In the same figure, we show the results obtained by substituting Eq. (15) into Eq. (12) using dashed lines. As long as the the domain size dependence of the diffusion coefficient can be approximated by Eq. (15), the size dependence of the coalescence rate is weak.

When $\nu R = 5$, the size dependence is weak even beyond the regime given by $\nu a \ll 1$. However, when $\nu R \geq 10$ and $\nu a > 0.1$ the coalescence rate decreases by increasing the domain size. In the figure, we show the results obtained by substituting Eq. (24) into Eq. (12) using dots. The coalescence rates with the full size-dependence of the diffusion coefficients [Eq. (14)] approach the results shown by dots as the size increases. The dots rapidly decrease by increasing the domain size because of the power-law dependence of the domain size in Eq. (24). When $\nu R \geq 10$ and $\nu a > 0.1$, the coalescence rate decreases by increasing the domain size because of the strong size dependence of the diffusion coefficient. If the coalescence rate decreases by increasing the size, the growth kinetics of the domain size should be suppressed. The growth law given by Eq. (20) and the result shown in Fig. 2 can be applicable when $\nu R = 5$, but should be applicable only when $\nu a \ll 1$ if the vesicle radius is large such as $\nu R \geq 10$.

We also note that the coalescence rate increases by increasing the domain size if the domain size becomes close to the vesicle radius. This dependence originates from the denominator of Eq. (12) and can be interpreted as the finite size effect of the domains confined in the spherical surface.

The diffusion coefficient Eq. (14) shows the logarithmic size dependence [Eq. (15)] and the power-law size dependence [Eq. (24)] as νa is varied. The dimensionless quantity νa characterizes the coupling between the embedding bulk fluid and the membrane for given size. The coupling is small when $\nu a \ll 1$. The domain growth and its asymptotic limit given by Eqs. (20) and (22), respectively, are obtained in the weak coupling limit. In the strong coupling limit $\nu a \gg 1$, the domain growth is suppressed as a result of the small coalescence rate compared to that in the weak coupling limit as shown in Fig. 2. The results are consistent with the simulation results that the growth law is suppressed by increasing the hydrodynamic coupling when the governing mechanism is DCC in 2D [7, 8].

The above conclusion is not altered if we use the diffusion coefficient for the solid domains instead of Eq. (14). Recently, the diffusion coefficient of the solid domain in the 2D flat membrane is approximated by a closed-form empirical expression [10]. The interpolation formula of the diffusion coefficient reproduces the logarithmic size dependence obtained from SD theory when $\nu a \ll 1$. When the interpolation formula is introduced, the coalescence rate Eq. (12) is slightly smaller but the overall size dependence is similar to that obtained by using Eq. (14). The coalescence rate decreases by the decrease of the diffusion coefficient of the solid domain compared to that of the liquid domain of the same size. In general, the diffusion coefficient of the solid domain is smaller than that of the liquid domain of the same size since the friction between the membrane and the solid edge is larger than that between the membrane and the liquid domain.

As shown above, the coalescence rate is constant in time when domains are confined on a spherical vesicle. The finite coalescence rate constant can also be calculated by considering a circular flat sheet of radius L by setting the absorbing boundary condition at $r = a$ and the reflecting boundary condition at $r = L$ ($a < L$). When a circular

domain of radius a is placed at the center of a circular flat sheet, the coalescence rate is given by Eq. (13) by replacing R with L [38]. Within this substitution, the domain size dependence of the coalescence rate is the same as that in a spherical vesicle. The diffusion coefficient of a domain placed at the center of a circular sheet of radius L was obtained by taking into account the viscosity of a circular flat membrane [1]. However, the result was limited for $a \ll L$ and obtained by ignoring the hydrodynamic coupling between the membrane and the solvent.

7. Discussion and conclusion

We discuss the relevant length scales in the recent experiment on domain growth kinetics by diffusion coalescence [14]. In the experiments, giant vesicles with a diameter of about 20 μm undergo phase separation at 30 °C after the temperature drop from the one-phase region (42–43 °C). The circular domains were observed when the size exceeded an optical resolution of the microscope (roughly 0.8 μm). In one of the coalescence processes, the large domains of the vesicle size appeared within several minutes. The domain growth by collision and coalescence was observed. In the other coalescence process, the domain growth was suppressed for several 10 minutes. The former process can be theoretically studied by assuming DCC.

The value of $\nu = 2\eta_{\rm s}/\eta$ can be estimated by using the typical values of $\eta_{\rm s} = 10^{-3}$ Pa·s, and η given by 0.1 Pa·s times the membrane thickness 5 nm as $\nu = 4.0 \times 10^6$ m^{-1}. We estimate $\nu R \approx 40$ by introducing the typical radius of the vesicles 10 μm. When $\nu R = 50$, the coalescence rate is almost independent of the domain size as long as $a < 25$ nm obtained from the condition of $\nu a < 0.1$. The domain size is much smaller than the optical resolution of the microscope such as 0.8 μm. Therefore, when the domain size grows and reaches to the optical resolution, the coalescence rate decreases with increasing the domain size and the domain growth can be suppressed compared to that given by Eq. (22). According to Fig. 3, the coalescence rate is almost constant over the wide range of the domain size when $\nu R = 5$. This value corresponds to the vesicle radius close to 1 μm which may be the maximum vesicle radius to observe the power-law growth given by Eq. (22).

It should be remembered that the full size-dependence of the diffusion coefficient for spherical vesicles is not known. In this paper, the size dependence of the coalescence rate has been discussed by substituting the known expression of the diffusion coefficient for 2D flat membranes. The full size-dependence of the diffusion coefficient for the spherical vesicle is needed to further develop the coagulation theory for the large domains within the current limit of optical resolutions.

In the original work by Yanagisawa *et al.*, the best fitted exponent 2/3 was obtained for the power-law domain growth [14]. However, the mechanism which leads to this large exponent is not well-understood. An attractive interaction between domains seems to be present due to the hydrodynamic flow around domains, which would accelerate the domain growth [39].

Power law growth of circular domains can be induced by transport of molecules from one domain to another through the medium [16, 40, 41, 42]. The growth of large domains is associated with evaporation of small domains, which is known as Ostwald ripening. According to the Lifshitz-Slyozov-Wagner theory of Ostwald ripening, the power law exponent is 1/3 [40]. In this paper, we studied the domain growth by the DCC mechanism and did not consider the evaporation and condensation mechanism in 2D. We just remark that the exponent 1/3 is independent of the dimensionality and holds also in 2D [8, 41, 42].

In conclusion, we have investigated DCC mechanism for growth kinetics of the liquid domains on the fluid vesicles. By applying the bimolecular reaction theory in the spherical surface and using the the 2D diffusion coefficient, the 2D coalescence rate is found to be independent of the liquid domain size if it is small enough. As a result, the domain size distribution is given by the classical Smoluchowski theory. When the circular shape is always maintained, we have obtained the mean domain size for the whole time range [Eq. (20)] by using the domain size distribution and the area conservation relation. In the asymptotic long time limit, we expect the power-law behavior with the exponent 1/2 [Eq. (22)].

The domain growth kinetics has been derived under the condition that the 2D coalescence rate is independent of the domain size. The condition is investigated by using recently obtained analytical expression for the diffusion coefficient of arbitrary domain size. When the vesicle radius is small, the coalescence rate can be well-approximated as a constant over the wide range of the domain size. When the vesicle radius is large, the coalescence rate becomes independent of the domain size only in the limit of the small domain size. In general, the coalescence rate decreases by increasing the domain size up to a certain size where the finite size effect dominates. The results are discussed in relation to the recent experimental observations of DCC in vesicles.

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Appendix A. The mean coalescence time

In this Appendix, we briefly present the derivation of Eq. (8) when the density satisfies Eqs. (2)–(5). The density can be expressed using the probability of finding a pair of domains at the relative position $\boldsymbol{r}$ at time t if their initial relative position was $\boldsymbol{r}_{\rm i}$ and was uniformly distributed

$$\rho_d(\boldsymbol{r},t) = \int \mathrm{d}\boldsymbol{r}_{\rm i}\, p_d(\boldsymbol{r},t|\boldsymbol{r}_{\rm i},0). \tag{A.1}$$

We introduce the survival probability that the pair has not coalesced up to time t if their initial relative position was $\boldsymbol{r}$

$$w_d(\boldsymbol{r},t) = \int \mathrm{d}\boldsymbol{r}_\mathrm{f}\, p_d(\boldsymbol{r}_\mathrm{f},t|\boldsymbol{r},0). \tag{A.2}$$

Because $p_d(\boldsymbol{r}_\mathrm{f},0|\boldsymbol{r},-t)$ satisfies the backward Kolmogorov equation and hence $p_d(\boldsymbol{r}_\mathrm{f},t|\boldsymbol{r},0) = p_d(\boldsymbol{r}_\mathrm{f},0|\boldsymbol{r},-t)$, we obtain [43, 44, 45]

$$\frac{\partial}{\partial t} w_d(\boldsymbol{r},t) = D_d \nabla^2 w_d(\boldsymbol{r},t), \tag{A.3}$$

with the initial condition

$$w_d(\boldsymbol{r},t=0) = 1, \tag{A.4}$$

and the boundary conditions

$$w_d(r=\sigma,t) = 0, \qquad \lim_{r\to\infty} w_d(r,t) = 1. \tag{A.5}$$

Since $1 - w_d(r,t)$ is the probability that the pair coalesce at time t, the mean coalescence time $\tau(r)$ is given by

$$\tau(r) = \int_0^\infty \mathrm{d}t\, t \frac{\partial}{\partial t}\left[1 - w_d(r,t)\right] = \int_0^\infty \mathrm{d}t\, w_d(r,t). \tag{A.6}$$

In general, the mean coalescence time is called the mean first-passage time. Integrating Eq. (A.3) over time and using Eq. (A.4), we find that the mean coalescence time satisfies Eq. (8) when domains are confined in the spherical surface. Note that in Eq. (A.3), the diffusion equation in the spherical surface can be written by assuming azimuthal symmetry such that

$$\begin{aligned} D_2 \nabla^2 w_2 &= D_2 \frac{1}{R^2 \sin\theta} \frac{\partial}{\partial \theta}\left(\sin\theta \frac{\partial w_2}{\partial \theta}\right) \\ &= \frac{D_2}{R^2} \frac{\partial}{\partial z}(1-z^2)\frac{\partial w_2}{\partial z}, \end{aligned} \tag{A.7}$$

where $z = \cos\theta$.

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